15TH ANNUAL

CARE™ AT ASH

CONFERENCE REPORT
SESSION SUMMARIES

AMERICAN SOCIETY OF HEMATOLOGY
DECEMBER 4TH, 2020

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The 15th annual CARE™ at ASH Meeting was virtually streamed on Friday, December 4th 2020. The event had a lineup of leading Canadian hematologists contextualize key news and data from the ASH 2020 Conference.

CARE™ at ASH 2020 Faculty:

**MEETING CO-CHAIR**

Dr. Diego Villa  
BC Cancer

Dr. Anca Prica  
Princess Margaret Cancer Centre

Dr. Chris Venner  
Cross Cancer Institute

**MEETING CO-CHAIR**

Dr. Martina Trinkaus  
University of Toronto

Dr. Wendy Lim  
McMaster University

Dr. Graeme Fraser  
Juravinski Cancer Centre

Dr. Julie Stakiw  
Saskatoon Cancer Centre

Dr. Denis Soulières  
CHUM

Dr. Kevin Hay  
BC Cancer

Thank you to all who tuned in! If you missed it, accessing the CARE™ at ASH virtual meeting content is as easy as ever! Conference details, speaker slides, navigation guide and on-demand presentations can all be found at: [https://careeducation.ca/events/agenda-care-at-ash-2020/](https://careeducation.ca/events/agenda-care-at-ash-2020/)

**Upcoming Programs in 2021**

The next virtual CARE™ Hematology meeting is set for February 2021 (CARE™ Winter Hematology Update)

The Regional CHC Quebec meeting (CCH QC) will take place in March 2021

Updates on programming tied to EHA and ASCO will follow.

For a comprehensive update of current and upcoming CARE™ programming please refer to: CAREeducation.ca/events/
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This report provides a review of relevant ASH plenary sessions and/or abstracts. The content and graphics included within each session summary were drawn from the presentations made by the respective speakers during the live CARE™ at ASH 2020 virtual stream.
Dr. Venner provided a review of practice changing data with daratumumab in AL amyloidosis. His updates in MM explored where the needle is in with frontline transplant eligible MM patients (and what data is needed to move it), and potential strategies to improve outcomes with pomalidomide-based therapies in the relapsed/refractory setting.

**AL Amyloidosis**

ASH 2020 Abstract 552. Reduction in Absolute Involved Free Light Chain and Difference between Involved and Uninvolved Free Light Chain Is Associated with Prolonged Major Organ Deterioration Progression-Free Survival in Patients with Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone with or without Daratumumab: Results from ANDROMEDA
Raymond L. Comenzo, et al.

Abstract Summary:
- A total of 388 patients were randomized to receive DARA-VCd (n=195) or VCd alone (n=193)
- Median follow-up was 11.4 months (range, 0.03-21.3+)
- The proportions of patients with heart and kidney involvement were 71% and 59%, respectively, and the proportions of patients with cardiac stage I, II, and IIIA were 23%, 40%, and 37%, respectively

Table. Rates of Hematologic Response and Treatment Group

<table>
<thead>
<tr>
<th>Hematologic response rate, %</th>
<th>VCd</th>
<th>DARA-VCd</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDROMEDA primary endpoint¹ ²</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>iFLC≤20 mg/L regardless of FLCr³</td>
<td>20</td>
<td>71</td>
</tr>
<tr>
<td>dFLC &lt;10 mg/L regardless of FLCr⁴</td>
<td>31</td>
<td>64</td>
</tr>
</tbody>
</table>

DARA-VCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; dFLC, difference between involved and uninvolved free light chain; FLCr, free light chain ratio; iFLC, involved free light chain; VCd, bortezomib, cyclophosphamide, and dexamethasone.

- MOD-PFS was longer in patients achieving deep hematological responses by all criteria
  - In addition, the corresponding MOD-PFS was similar regardless of the hematological response criteria used

Conclusions and CARE™ Faculty Canadian Perspectives

Regardless of the criteria used, the addition of DARA to VCd increased the rates of deep hematologic responses in patients with newly diagnosed AL amyloidosis, which, in turn, was associated with prolonged MOD-PFS. Depth of response in amyloidosis is CRUCIAL! It is reflective of ability to “turn the tap off”, important in improving organ function long-term, and important for clonal control and prevention of future relapse.

Further data to look out for includes specific organ responses based on baseline involvement and clarification of which progression events were death. This is a key outcome in amyloid studies as early death is common, and patients have to live long enough to hit maximal clonal response and benefit from the response. Long-term data on durability is still lacking but daratumumab should be considered a standard option based on the remarkable data to date.
Frontline Transplant Eligible MM (TEMM)

ASH 2020 Abstract 142. Upfront Autologous Hematopoietic Stem-Cell Transplantation Improves Overall Survival in Comparison with Bortezomib-Based Intensification Therapy in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the Randomized Phase 3 EMN02/HO95 Study
Cavo et al.

ASH 2020 Abstract 550. Consolidation Treatment with VRD Followed By Maintenance Therapy Versus Maintenance Alone in Newly Diagnosed, Transplant-Eligible Patients with Multiple Myeloma (MM): A Randomized Phase 3 Trial of the European Myeloma Network (EMN02/HO95)
Sonneveld et al.

Abstract Summary:
- EMN02 examined two main questions after CyBorD induction and incorporation of len mant:
  1. Role of transplant (R1)
  2. Role of RVD consolidation (R2)

Figure. OS with ASCT vs. VMP (Cavo et al)

![Image of OS with ASCT vs. VMP](image)

Conclusions and CARE™ Faculty Canadian Perspectives

Data as presented indicates that ASCT is important and improves OS, consolidation improves PFS, and benefit is present regardless of R-ISS stage, in standard risk CG, and regardless of ASCT vs VMP.

Outstanding questions remain on:
- Magnitude of benefit in ASCT cohort (CyBorD/ASCT/RVD/Len maint vs. CyBorD/ASCT/Len maint)
- Are either/both comparable to Canadian standard CyBorD/ASCT (single)/Len maint? (Median PFS ~ 58 months)
- Are either comparable to other novel frontline approaches?
  - FORTE (KRD/ASCT/KRD/R+-K)- see ASH 2020 update below
  - GRIFFIN (especially the control arm of RVD/ASCT/RVD/R)- see ASH 2020 update below
ASH 2020 Abstract 141. Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial Gay et al.

Abstract Summary:
- Data cut-off was June 30, 2020
- 474 NDMM pts were randomized (KRd_ASCT, n=158; KRd12, n=157; KCd_ASCT, n=159) and analyzed. Pt characteristics were well balanced
- After a median follow-up from R1 of 45 m, median PFS was not reached with KRd_ASCT, 57 m with KRd12 and 53 m with KCd_ASCT (KRd_ASCT vs KCd_ASCT: HR 0.53, P<0.001; KRd_ASCT vs KRd12: HR 0.64, P=0.023; KRd12 vs KCd_ASCT: HR 0.82, P=0.262)
- 3-year overall survival (OS) was 90% with KRd_ASCT and KRd12 vs 83% with KCd
- After a median follow-up from R2 of 31 m and a median duration of maintenance of 27 m in both arms, 46% of MRD-positive pts at randomization turned negative in KR vs 32% in R (P=0.04)
- By ITT analysis, 3-year PFS from R2 was 75% with KR vs 66% with R (HR 0.63, P=0.026). The benefit of KR vs R was observed in most subgroups (Figure). 3-year OS was 90% in both arms
- During maintenance, a similar proportion of pts experienced ≥1 grade (G)3-4 hematologic adverse events (AEs)/serious AEs (SAEs) in the 2 arms (KR 22% vs R 23%)
  - Most frequent were neutropenia (KR 18% vs R 21%) and thrombocytopenia (KR 3% vs R 3%)
  - Dose reductions of R were reported in 23% of KR and 29% of R pts; dose reductions of K were reported in 20% of pts. The rate of discontinuation due to AEs was similar in the 2 arms (KR 10% vs R 9%)

Conclusions and CARE™ Faculty Canadian Perspectives

Like EMN02, these data support ASCT vs non-ASCT options. Interestingly the control arm of KCD/ASCT/KCD maintenance gives a lesser median PFS than Canadian standard (CyBorD), thus the question is whether KRD/ASCT/KRD/maint is markedly better than 58 months, and if so, if it is because of KR maintenance or R maintenance.

This brings to question what is driving the difference in KR vs R maintenance? To answer this we need to look at the breakdown of all 6 cohorts and to pay attention to the tail of the curves (i.e. proportion of long-term survivors)


Abstract Summary:
- Randomized phase 2 study looking at RVD/ASCT/RVD/R maintenance vs. Dara-RVD/ASCT/Dara-RVD/Dara-R maintenance
- 207 patients were randomized (D-RVd, n=104; RVd, n=103)
- At the end of post-transplant consolidation (median follow-up, 13.5 months) in the response-evaluable population, the sCR rate favored D-RVd versus RVd (42.4% [42/99] vs 32.0% [31/97]; 1-sided P=0.0680)
- At the 12-months-of-maintenance therapy data cut (median follow-up, 26.7 months), the sCR rate still favored D-RVd versus RVd (63.6% [63/99] vs 47.4% [46/97], 2-sided P=0.0253 (Figure)
- No new safety concerns were observed with longer follow-up
Conclusions and CARE™ Faculty Canadian Perspectives

The addition of daratumumab to RVd induction and consolidation, followed by D-R maintenance in patients with transplant-eligible NDMM demonstrated deep and improved responses, including higher sCR and MRD negativity rates, compared with lenalidomide alone. Maintenance therapy increased sCR and MRD negativity rates, compared to post-consolidation rates.

While still early, these date are exciting given the unprecedented level of response. It will be interesting to see how response will translate to PFS (Estimated 24-month PFS rates in this study were 94.5% and 90.8% for the D-RVd and RVd groups, respectively).

We still await a clear winner for ideal treatment in TEMM and PFS/OS will likely be needed to move the needle.

Improving Pomalidomide-based Therapies in Relapsed/Refractory (R/R) MM

ASH 2020 Abstract 412. Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide (Pom) and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with R/R MM

Dimopoulos, et al.

Abstract Summary:

- 304 pts from 12 European countries were randomized (151 D-Pd; 153 Pd)
- Key to interpreting relapsed trials is inclusion/exclusion criteria and preceding treatment history:
  - 45%/33%/22% pts were ISS stage I/II/III
  - 35% had high cytogenetic risk (presence of del17p, t[14;16], or t[4;14])
  - ≥ 1 prior line of therapy
  - 11% of pts had received 1PL (median [range] prior lines of therapy = 2 [1-5])
  - 79.6% of pts were refractory to len
  - 48.0% of pts were refractory to a PI
  - 42.4% of pts were refractory to both
  - Median duration of treatment was 11.5 months with D-Pd vs 6.6 months with Pd
- Median duration of treatment was 11.5 months with D-Pd vs 6.6 months with Pd
- Primary analysis was performed after 190 PFS events
- The median PFS for the D-Pd vs Pd arms was 12.4 vs 6.9 months, respectively (HR = 0.63 (95% CI, 0.47-0.85; P=0.0018))
- Response: ≥CR = 24.5% vs 3.9%; ≥VGPR = 51.0% vs 19.6%
- No new safety concerns were observed

**Conclusions and CARE™ Faculty Canadian Perspectives**

In this study the IRR rate was very low and administration duration short, thus increasing convenience for patients and decreasing treatment burden. These data are clinically relevant and demonstrate that D-Pd is an effective and convenient treatment for R/R MM who received ≥1 prior therapy, including len and a PI.

Which patients this will be used in (when it might finally be approved 3 years from now) with daratumumab exposure earlier in therapy remains to be seen.

**Related Abstracts of Interest:**

ASH 2020 Abstract 413. A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma
Sebag, et al.

ASH 2020 Abstract 725. Part 1 Results of a Dose Finding Study of Belantamab Mafodotin (GSK2857916) in Combination with Pomalidomide (POM) and Dexamethasone (DEX) for the Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)
Clinically Relevant Abstract
Trudel, et al.

Novel CART and BiTE approaches with immune novel targets are coming and numerous early phase studies and a whole section at ASH 2020 was dedicated to these approaches in MM (ASH 2020 session 653. Myeloma/Amyloidosis: Novel Therapies Targeting B Cell Maturation Antigen in Relapsed/Refractory Multiple Myeloma; CAR T Therapies for Myeloma- Novel Approaches and Longer-Term Follow Up Data)

**Additional Resource *Coming Soon!*:**

CARE™ MM Guidance- Navigating the New Normal in 2021

Changes in the delivery of care brought on by the pandemic have happened fast, despite not necessarily being optimal for patient outcomes. These changes, as well as increased complexity with MM treatment decisions with availability of novel agents have prompted the CARE™ Faculty to create the CARE™ MM Treatment Guidance: Navigating the New Normal in 2021.

This is the 1st iteration (V.1) of the CARE™ MM Treatment Guidance. Stay tuned to access the full Guidance and recommendations for R/R MM!
This section provides a summary of relevant data from ASH in CLL, in the context of the following outstanding questions:

1. Can we improve upon BTKi monotherapy?
   - Selective BTKi (acalabrutinib, zanubrutinib) to possibly reduce toxicity
   - Reduce emergence of resistance associated with covalent BTKi (LOXO-305)
   - Combination regimens

2. Indefinite vs time-limited therapy
   - What are the long-term outcomes with time-limited approaches?
   - Can MRD status guide therapy?

**Improving on BTKi Monotherapy**

ASH 2020 Abstract 2219. Long-Term Efficacy of First-Line Ibrutinib Treatment for Chronic Lymphocytic Leukemia (CLL) With 4 Years of Follow-Up in Patients With TP53 Aberrations (del(17p) or TP53 Mutation): A Pooled Analysis From 4 Clinical Trials

John N. Allan, et al.

Abstract Summary:

- Data for first-line ibrutinib treatment in pts with TP53 aberrations were pooled across 4 clinical trials in CLL/SLL: PCYC-1122e (NCT01500733; single-agent ibrutinib; n=34), PCYC-1130 (NCT02264574; ibrutinib + obinutuzumab; n=18), ECOG1912 (NCT02048813; ibrutinib + rituximab; n=26), and RESONATE-2 (NCT01722487; single-agent ibrutinib; n=11)
- Eighty-nine pts with TP53 aberrations receiving first-line ibrutinib treatment were included
- With a median follow-up of 50 months (range 0.1 to 95.9 months), median PFS was not reached (95% CI: 67 months to not estimable)
- Although pts with TP53 aberrations remain at risk for progression, first-line treatment with ibrutinib has partially overcome the poor prognosis in this high-risk population with 4-year PFS and OS rates of 79% and 88%, respectively
- No new safety signals were identified in this analysis

**Conclusions and CARE™ Faculty Canadian Perspectives**

With a median follow-up of 4 years, first-line ibrutinib-based treatment resulted in sustained long-term efficacy with high PFS and OS rates in CLL pts with TP53 aberrations, a population with historically poor outcomes.

These results support our current practice with ibrutinib as a standard of care for patients with TP53 deletion/mutation. For the small group of CLL patients that may be candidates for allogeneic SCT, these data also support the Canadian practice of SCT deferral to relapse.
Figure. Study Design

- Of 36 pts with at least 16 mo. of follow-up, the overall response rate is 100% (43% CR/CRi, 57% PR [in most cases due to small residual lymph nodes]), with 31% BM-uMRD CR at C16 (primary endpoint).
- By ITT at C16, 84% PB-uMRD and 78% BM-uMRD.
- Eleven pts in BM-uMRD CR discontinued therapy as allowed per protocol after 15 cycles.
- Median time off therapy for these pts is 4 mos (range: 1-10). No pts have progressed to date.
- Reported toxicities:
  - Grade 1/2 non-heme toxicity: headache (78%), fatigue (75%), bruising (57%), nausea (45%), rash (32%), diarrhea (27%)
  - Grade 3/4 heme toxicity: neutropenia (34%), thrombocytopenia (23%)
  - AF (2%), TLS (4.5% - after obin), no cases of febrile neutropenia, one case gr 3 pneumonia

Related Abstracts of Interest:

Abstract 2223. Evaluation of the Incidence and Risk Factors Associated with Major Cardiovascular Events (MACE) in Patient Receiving Acalabrutinib Therapy (Azali et al.)

Abstract 1306. Efficacy and safety of Zanubrutinib in Patients with Treatment-Naïve CLL/SLL with del17p: Follow-up results from Arm C of the SEQUOIA Trial (Brown et al.)

Abstract 123: Ibrutinib Plus Venetoclax for First-Line Treatment of CLL/SLL: 1 yr DFS Results from the MRD Cohort of the Phase 2 CAPTIVATE Study (Wierda et al.)
The AVO triplet is highly active, achieving BM-uMRD after 15 months of time-limited therapy in a frontline CLL population that included nearly 40% pts with TP53 aberrant disease.

Selective BTKi appears likely to have reduced toxicity compared to ibrutinib based upon point estimates in non-comparative trials, however head-to-head comparisons are needed to provide more information on this. Longer-term data is needed with these new BTKis and clinical use of MRD testing will require further assessment in phase III trials (a registrational phase 3 trial CL-311, NCT03836261, is underway).

Currently, ibrutinib is the only funded novel agent in the frontline setting. Acalabrutinib and venetoclax+ obinutuzumab will hopefully be available soon (for fludarabine ineligible patients).

ASH 2020 Abstract 542. LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results from the Phase 1/2 BRUIN Study

Anthony R. Mato et al.

Abstract Summary:
- LOXO-305 is a selective, non-covalent BTKi able to inhibit wild type BTK and the C481 BTK mutant equally in vitro
- Phase I/2 trial in B cell malignancies (CLL = 94)
- Median age was 69, median prior therapies = 4 (BTKi 84%, ven 31%, PI3Ki 20%), del17p 21%, TP53m 30%
- No DLT’s or dose reductions; RP2D = 200mg PO OD
- TEAE’s > 10% were fatigue (16%) and diarrhea (15%)
- ORR was 77% for patients with > 6 months on treatment
  - ORR WT = C481

Related Abstracts of Interest:
Abstract 2225. Rarity of BCR-pathway mutations in progression free patients with CLL during 1st line vs Rel/Ref treatment with ibrutinib
Wiestner et al.

Abstract 524. High Clonal Complexity of Resistance Mechanisms Occurring at Progression after Single Agent Targeted Therapy Strategies in CLL
Thompson E. et al.

Our understanding of resistance mechanisms and their clinical impact continues to evolve however testing is not routinely available at most Canadian centres.

LOXO-305 and other agents developed with the aim of reducing toxicity and drug resistance may be a focus of upcoming clinical trials in Canada.
Long-term Outcome with Time-Limited Approaches

ASH 2020 Abstract 125 Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Arnon P. Kater et al.

Abstract Summary:
- Long-term MRD kinetics and updated efficacy outcomes, including re-exposure to VenR (to be presented), with a 5 year (yr) median follow-up (clinical cutoff date May 8, 2020)
- 389 pts were enrolled (VenR, n=194; BR, n=195). With a median f/u of 59.2 (range, 0–71.5) mo, the PFS benefit with VenR over BR was sustained (HR, 0.19 [95% CI: 0.15–0.26]; p<0.0001)
- Median PFS was 53.6 months with VenR
- Improved OS outcome was observed among the VenR pts that reached end of treatment (EOT) without PD and had uMRD (83/118) compared with those with MRD (35/118), with 3-yr post-EOT survival estimates of 95.3% (95% CI: 90.0–100.0) vs 85.0% (95% CI: 72.8–97.2), respectively
- Median time to MRD conversion from EOT was 19.4 (95% CI: 8.7–28.3) mo
- Those most at risk of conversion had high risk features, including uIGHV (see table)

Table. MRD Conversion and PD Status According to Patients Genetic Profile Status

<table>
<thead>
<tr>
<th></th>
<th>del(17p) n (%)</th>
<th>GC (≥3 CNV) n (%)</th>
<th>IGVH n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes BEP: n=4</td>
<td>No BEP: n=54</td>
<td></td>
</tr>
<tr>
<td>Sustained uMRD</td>
<td>0 (0)</td>
<td>21 (39)</td>
<td>20 (36)</td>
</tr>
<tr>
<td>Conversion to MRD (no PD)</td>
<td>0 (0)</td>
<td>21 (39)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Conversion with subsequent PD</td>
<td>4 (100)</td>
<td>12 (22)</td>
<td>21 (37)</td>
</tr>
</tbody>
</table>

BEP, biomarker evaluable population; CNV, copy number variations; del(17p), chromosome 17p deletion; GC, genomic complexity; IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; mut, mutated; uMRD, undetectable minimal residual disease; unmut, unmutated; PD, progressive disease; pts, patients.

Related Abstract of Interest:

Abstract 3139. Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration Venetoclax in the Murano Study

Conclusions and CARE™ Faculty Canadian Perspectives

The MURANO 5 year follow up data demonstrate durable OS benefit and PFS benefit compared to CIT in relapsed CLL, supporting Ven+R as a standard treatment option. Comparisons to indefinite BTKi monotherapy and data regarding Ven+R after BTKi therapy remain lacking.

Responses to novel agents following venetoclax (abstract. 3139) provide reassurance, however longer-term follow-up is needed and criteria for venetoclax retreatment bear monitoring in an era of increased frontline BTKi.
**Additional Resource *Coming Soon!*:**

**CARE™ CLL Guidance - Navigating the New Normal in 2021**

New drug approvals and updated indications, availability of trial data relating to sequencing, and changes in delivery of CLL patient care brought on by the COVID-19 pandemic have prompted the CARE™ Faculty to update the CARE™ CLL treatment Algorithm. This is the 3rd iteration of the CARE™ CLL Treatment Guidance, first developed and distributed in 2018.

What follows is a snapshot of the updated frontline Algorithm- Stay tuned to access the full Guidance and recommendations for R/R CLL and additional information and context from the CARE™ CLL Faculty!
Dr. Prica reviewed key publications and abstracts from ASH in two key areas:

- Frontline aggressive lymphomas – CNS prophylaxis
- Early-stage Hodgkin lymphoma

A summary of the abstracts and Dr. Prica’s observations from a Canadian perspective follow.

**Aggressive Lymphomas**

ASH 2020 Abstract 477. Lack of Effectiveness of Intravenous High-Dose Methotrexate for Prevention of CNS Relapse in Patients with High-Risk DLBCL: A Retrospective Analysis from Alberta, Canada

*Robert Puckrin et al.*

**Abstract Summary:**

- Retrospective 2012-2019, 906 pts DLBCL pts with 18-70 yrs of age
- From 2015 - HD-MTX 3.5g/m2 IV after cycles 2, 4, and 6 of R-CHOP: CNS-IPI 4-6, double hit lymphoma, or testicular involvement
- Median follow-up time was 35.3 months (range 0.29-105.7)
- Risk of CNS relapse was 1.9% (95% C.I. 0.0-30.7%) for patients with CNS-IPI 0-1, 4.9% (95% C.I. 0.5-18.0%) for CNS-IPI 2-3, and 12.2% (95% C.I. 4.0-25.2%) for CNS-IPI 4-6 (p<0.0001)
- Risk of CNS relapse was significantly increased for patients meeting APLCPG high-risk criteria (11.8% vs 3.0%, p<0.0001)

**Table:** Multivariate analysis of NCS relapse, PFS, and OS by treatment arm in APLCPG high-risk patients, controlling for CNS-IPI score, double-hit lymphoma, and testicular involvement (n=326)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
<th>P value</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
<th>P value</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
<th>P value</th>
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<tbody>
<tr>
<td>HD-MTX prophylaxis</td>
<td>1.61</td>
<td>0.72-3.59</td>
<td>0.25</td>
<td>1.06</td>
<td>0.71-1.58</td>
<td>0.78</td>
<td>1.12</td>
<td>0.72-1.75</td>
<td>0.61</td>
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<tr>
<td>Higher intensity chemotherapy</td>
<td>0.38</td>
<td>0.08-1.95</td>
<td>0.25</td>
<td>0.59</td>
<td>0.30-1.18</td>
<td>0.14</td>
<td>0.63</td>
<td>0.29-1.37</td>
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<td>Consolidative autotransplant</td>
<td>0.30</td>
<td>0.09-1.01</td>
<td>0.051</td>
<td>0.41</td>
<td>0.24-0.71</td>
<td>0.001</td>
<td>0.56</td>
<td>0.32-0.98</td>
<td>0.043</td>
</tr>
</tbody>
</table>


*Victor M. Orellana-Noia et al.*

**Abstract Summary:**

- 1030 patients met eligibility, with median follow-up of 2.3 years
- FL regimens included RCHOP (45.9%), REPOCH (46.5% total; 79.1% with dose-adjustment), 7.6% other
- Prophylaxis (PPx) was given intravenously (IV) in 20% of pts vs 77% intrathecally (IT), over a median 2.9 vs 4.1 doses respectively
- CNSrel after FL treatment was 5.3% overall without significant difference by PPx route (7% IV vs 5% IT, p=0.178)
- There was no significant difference in anatomic site(s) of CNSrel by PPx route
- Rates of CNSrel were significantly higher with CNS-IPI high vs moderate risk (8.3 vs 4.1%, p=0.03), elevated LDH (6.9 vs 2.6%, p=0.007) and multiple inv EN sites (7.5% for 2+ vs 4% for 0-1, p=0.01); each additional EN site further increased risk (p=0.03 for trend)
- Median PFS and OS for the overall group have not been reached; 2-yr PFS and OS were 70 and 85% respectively. PFS and OS were each predicted by CNS-IPI (p<0.0001)
- In those with CNSrel, subsequent relapse and/or death was common (n=41, 74.5%) regardless of initial PPx route or salvage tx. Median survival after CNSrel diagnosis was poor (7.1 months, range 1 day-5.3 yrs) and was significantly inferior to those with non-CNSrel (HR 1.488, p=0.03)
- Use of single-route ppx demonstrated similar CNSrel vs established outcomes for this population in the rituximab era, with no difference by PPx route

ASH 2020 Abstract 530. Cerebrospinal Fluid (CSF) Analysis of Tumor-Specific Cell-Free DNA (cfDNA) As a Diagnostic and Prognostic Tool for Central Nervous System (CNS) Invasion in Lymphoma
Adam J Olszewski et al.

Abstract Summary:
- To examine the diagnostic sensitivity of the NGS-MRD assay in the CSF, CSF from 6 pts with lymphomas who had known parenchymal or leptomeningeal CNS invasion was prospectively collected. Stored DNA from historical CSF samples of 8 pts with CNS lymphoma who tested negative by conventional IGH-PCR was also tested

Figure. Alluvial plot showing patient cohorts in study, their CNS invasion status, result of the CSF NGS-MRD assay, and subsequent CNS relapse

- For patients with CNS parenchymal disease, median cfDNA copy count in the CSF fluid was 2 /mL (range, 0.4-929) and median clonotype frequency was 9.0% (range, 0.03-68.9%)
- For patients with leptomeningeal disease, these values were 2233 /mL (1.2-5620) and 37% (1.7-98.4%), respectively
- With median follow-up of 11 months, no pts with negative baseline NGS-MRD assay in CSF relapsed, whereas 2 of 10 with a positive assay had a CNS relapse (12-month incidence, 29%)
- In this proof-of-concept study, the NGS-MRD CSF assay showed 100% sensitivity for diagnosing intraparenchymal CNS invasion in aggressive lymphomas that were not detected in the CSF using conventional methods
  - The 100% sensitivity and 100% negative predictive value of the assay for subsequent CNS relapse warrants further prospective evaluation as a potential tool for personalizing CNS-directed prophylaxis
ASH 2020 Abstract 708 Outcome Among Adolescents and Young Adults with Mature B-Cell Non-Hodgkin Lymphoma at Pediatric Versus Adult Centers: A Population-Based Study Using the IMPACT Cohort

Sumit Gupta et al.

Abstract Summary:

- The IMPACT cohort comprises all Ontario, Canada AYA aged 15-21 years diagnosed with one of six common cancers (including NHL) between 1992-2012
- Among 176 AYA with B-NHL, 62 (35.2%) received therapy at a pediatric center

Table. Event-free and OS by locus of care among AYA with mature B-cell NHL

<table>
<thead>
<tr>
<th>Therapy Location</th>
<th>Event-free Survival</th>
<th>OS Survival</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Center</td>
<td>5-year (±standard error)</td>
<td>82.3±4.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Adult Center</td>
<td>5-year (±standard error)</td>
<td>66.7±4.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>Pediatric Center</td>
<td>5-year (±standard error)</td>
<td>85.5±4.5%</td>
<td>0.03</td>
</tr>
<tr>
<td>Adult Center</td>
<td>5-year (±standard error)</td>
<td>71.1±4.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Pediatric Center</td>
<td>5-year (±standard error)</td>
<td>83.3±6.2%</td>
<td>0.04</td>
</tr>
<tr>
<td>Adult Center</td>
<td>5-year (±standard error)</td>
<td>66.7±4.9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Pediatric Center</td>
<td>5-year (±standard error)</td>
<td>88.9±5.2%</td>
<td>0.04</td>
</tr>
<tr>
<td>Adult Center</td>
<td>5-year (±standard error)</td>
<td>72.0±4.7%</td>
<td>0.04</td>
</tr>
<tr>
<td>Pediatric Center</td>
<td>5-year (±standard error)</td>
<td>80.8±7.7%</td>
<td>0.20</td>
</tr>
<tr>
<td>Adult Center</td>
<td>5-year (±standard error)</td>
<td>66.7±10.3%</td>
<td>0.25</td>
</tr>
</tbody>
</table>

- Further confirmatory studies are warranted, as are studies to determine the relative contribution of pediatric protocols versus other components of care

Conclusions and CARE™ Faculty Canadian Perspectives (Aggressive Lymphoma)

We can reliably identify aggressive B-cell lymphoma patients at higher risk of CNS relapse. However, it does not seem like CNS directed prophylaxis, even systemic, necessarily changes that risk. Better systemic disease control and diagnosis of minimal involvement of CSF is needed to decrease the risk in high-risk patients, including novel regimens for pts with CNS involvement.

Similar to ALL, it is intriguing to consider that AYA DLBCL patients (up to 21 yrs. of age) have worse outcomes with adult protocols (mostly RCHOP), which brings to question whether we should we be considering pediatric protocols.

Early Unfavourable Hodgkin lymphoma (HL)

ASH 2020 Abstract 2065 Prognostic Impact of PET after 2 Cycles of Escalated Beacopp Plus 2 Cycles of ABVD on Progression Free Survival in Early Unfavourable Hodgkin Lymphoma within the Phase 3 GHSG HD17 Trial

Michael Fuchs et al.

Abstract Summary:

- Between January 2012 and March 2017, 1100 patients with newly diagnosed early-stage unfavourable HL aged 18-60 years from Germany, Switzerland, Austria and the Netherlands were recruited for this randomized, parallel-group phase 3 trial
- Primary objectives included non-inferiority of the chemotherapy-alone treatment in PET-negative patients and the impact of a positive PET-finding on the outcome in terms of progression free survival (PFS)
- Among 979 randomized patients with regular PET after 2+2 651 (67%), 238 (24%) and 90 (9%) had DS1-2, 3 and 4 respectively
- Median observation time was 45 months for PFS and 47 months for overall survival (OS)
- The 5-year PFS difference between the two groups was -2.2% (95% CI, -5.3% to 0.9%) excluding the lower margin of -8%
Overall survival rates at 5 years were 98.8% in the standard group and 98.4% in the PET guided group.

Importantly, radiotherapy can be safely omitted without compromising the very good PFS and OS in these patients with newly diagnosed early unfavourable HL.

Conclusions and CARE™ Faculty Canadian Perspectives

For early-stage, unfavourable HL patients, 2escBEACOPP + 2 ABVD with radiation omission if PET negative is very attractive, especially in young patients with large radiation fields. An individualized approach for each patient with multidisciplinary discussion from the start with rad onc colleagues is required.

Other Abstracts of Interest in HL

ASH 2020 Abstract 1157. PVAG Regimen (Prednisone, Vinblastine, Doxorubicin, Gemcitabine) Used in Real-Life Setting in First Line Therapy for Elderly Classical Hodgkin Lymphoma Patients: A Retrospective Study of Lysa Centers
Guillaume Aussedat et al.

ASH 2020 Abstract 471. Frontline Brentuximab Vedotin As Monotherapy or in Combination for Older Hodgkin Lymphoma Patients
Christopher A. Yasenchak, et al.
**IMMUNOTHERAPY**

**DR. KEVIN HAY / BC CANCER**

Full presentation slides and On Demand video content can be accessed at: [https://careeducation.ca/events/care-at-ash-on-demand-dr-graeme-fraser/](https://careeducation.ca/events/care-at-ash-on-demand-dr-graeme-fraser/)

Immunotherapy is a broad field with a number of sessions across multiple categories focused on these novel therapies. Dr. Hay focused on cellular immunotherapy and how new approaches to cell therapy are changing and improving on various steps involved in delivery of cellular therapies (see figure below for examples of these potential new strategies).

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**Indolent Lymphoma**

ASH 2020 Abstract 700. Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)

Caron Jacobson et al.

Abstract Summary:

- 146 patients with iNHL (124 FL; 22 MZL) received axi-cel; 84 patients with FL had ≥ 12-months follow-up
  - Axi-cel was successfully manufactured for all enrolled patients
  - Median follow-up was 17.5 months (range, 1.4 - 31.6)
  - ORR was 92% among efficacy-evaluable patients with iNHL (n = 104), with a 76% CR rate
  - In patients with FL (n = 84), the ORR was 94% (80% CR rate); in those with MZL (n = 20), the ORR was 85% (60% CR rate)
  - The medians for DOR, PFS, and OS were not reached; 12-month estimated rates were 72% (95% CI, 61 – 80), 74% (95% CI, 63 – 82), and 93% (95% CI, 86 – 97), respectively
  - Grade ≥ 3 AEs occurred in 86% of patients with iNHL (85% in FL; 95% in MZL), most commonly neutropenia (33%), decreased neutrophil count (27%), and anemia (23%)
  - Grade ≥ 3 cytokine release syndrome (CRS; per Lee, et al, Blood. 2014) occurred in 7% of patients with iNHL (6% in FL; 9% in MZL)
  - Grade ≥ 3 neurologic events (NEs; per CTCAE v4.03) occurred in 19% of patients with iNHL (15% in FL; 41% in MZL)
  - Most CRS (118/119) and NEs (81/87) of any grade resolved by data cutoff
  - The median peak CAR T cell level was 38 cells/µL (range, 0 – 1415) in all treated patients with iNHL

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Conclusions and CARE™ Faculty Canadian Perspectives

Patients with advanced stage iNHL are incurable with standard therapies, and the disease can take a more aggressive approach in some patients, underscoring a need for novel therapies.

Axi-cel appears to be safe and effective for the treatment of indolent lymphoma that has not responded to other treatments. This study demonstrates that ORR and CR rates are better than in DLBCL, however, only 62% have ongoing responses.

Questions remain:
• Will some patients have a long-term cure from CAR-T cells?
  • Will we see a plateau in the PFS/OS curves?
• At what stage should this therapy be used in the future?
  • Anticipate there is a role in patients who are refractory to last therapy or who have experienced progression of disease within 2 years
• What is the cost for Canadian system?

Mantle Cell Lymphoma

ASH 2020 Abstract 118. Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in Transcend NHL 001
Maria Lia Palomba et al.

Abstract Summary:
• Primary endpoints were safety and objective response rate (ORR); Secondary endpoints CR, duration of response, PFS, and OS
• 41 patients had undergone leukapheresis and 32 had received liso-cel (DL1, n = 6; DL2, n = 26).
• Of 28 patients (87.5%) who had received a prior Bruton tyrosine kinase inhibitor, 11 (34%) were refractory to the therapy.
• Seventeen patients (53%) received bridging therapy.
• 16 patients (50%) had cytokine release syndrome (CRS), including 1 grade 4 event (3%); 9 patients (28%) had neurotoxicity, with 3 grade 3 events (9%)
• 27 responded to liso-cel (ORR, 84%: DL1, n = 4/6 [67%]; DL2, n = 23/26 [88%]), and 19 (59%) achieved a CR (DL1, n = 2/6 [33%]; DL2, n = 17/26 [65%])
• 20 of 27 responders had an ongoing response at last data cut, but median follow-up duration is short (10.9 [1.2–24.8] months for DL1 and 3.1 [0.4–23.0] months for DL2)

Conclusions and CARE™ Faculty Canadian Perspectives

These findings confirm that liso-cel works in mantle cell lymphoma. There are definitely patients in Canada who could benefit from this therapy, and will likely have a role after failure of BTKi

Questions remain:
• What is the BMS plan for liso-cel and MCL in Canada?
• How does this timeline fit with Kite/Gilead plans for brexucabtagene autoleucel?
  • The ORR 88% and CR 65% at optimal DL (DL2) is roughly comparable
  • Seems to have a lower rate of severe CRS/ICANS than brexucabtagene autoleucel
  • We will likely never have a head-to-head trial with these two agents
Frontline DLBCL

ASH 2020 Abstract 405. Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in Patients with High-Risk Large B Cell Lymphoma (LBCL)
Sattva S. Neelapu et al.

Abstract Summary:
- The primary endpoint was investigator-assessed CR rate; secondary endpoints were ORR and AEs
- 31 pts have been enrolled and treated, 15 pts with ≥ 3 months of follow-up
  - 60% had double- or triple-hit status per investigator, and 67% had IPI score ≥ 3
  - Lower median tumor burden in ZUMA-12 (ZUMA-1: 3897 mm² vs ZUMA-12: 1610 mm²)
- 12 response-evaluable patients the ORR was 92% with a CR rate of 75%
- 15 safety-evaluable patients, Grade ≥ 3 CRS and neurologic events (NEs) occurred in 20% and 27% of patients, respectively

Conclusions and CARE™ Faculty Canadian Perspectives

High-risk LBCL has poor outcomes with R-CHOP chemoimmunotherapy and ~50% of patients will not achieve long-term disease remission. Axi-cel appears to be safe and effective in DLBCL not responding early to frontline R-CHOP

Questions Remain:
- Axi-cel is Health Canada approved already for DLBCL in third line- will it be approved (and funded) in front-line, and if so, what is the impact on subsequent lines?
- R-CHOP is such a gold standard, with multiple attempts to improve on this, what will be needed for this to be adopted in this setting?
  - The answer is likely phase III data
- Can we further refine the patients who would benefit?

It will be interesting to see the results of ZUMA-7 (second line, transplant eligible) to put all this in context

Presentation Now Available for Viewing!
Click Here to access presentation on the important role nurses play regarding CAR T
Myeloma

ASH 2020 Abstract 177. CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma

Deepu Madduri, MD et al.

Abstract Summary:

- The primary objective of the phase 1b portion was safety and establish RP2D; the primary objective of the phase 2 portion was to evaluate cilta-cel efficacy
- 97 pts with R/R MM received cilta-cel (29 in phase 1b: 68 in phase 2)
- Median follow-up duration was 8.8 mo (range 1.5–20.4)
- ORR 94.8%, with a sCR 55.7%, VGPR 32.0%, and PR rate of 7.2%
- Median time to first response was 1.0 mo (range 0.9–5.8; 80.4% ≤1.0 mo), and median time to complete response or better was 1.8 mo (range 0.9–12.5; 74.1% ≤3.0 mo)
- Of 52 MRD-evaluable pts, 94.2% were MRD-negative at 10-5
- The 6-mo PFS 87.4% and OS 93.8%
- CRS in 94.8% of pts (grade 3/4 4.1%), ICANS in 20.6% of pts (gr 3/4 10.3%)

Conclusions and CARE™ Faculty Canadian Perspectives (Abstract 177)

Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor T (CAR-T) cell therapy with 2 BCMA sdAbs designed to confer avidity. Most notably from this trial, CRS rate appears high, but serious events are low.

Questions Remain:

- Is there an eventually plateau in the PFS / OS curves?
  - Longer follow-up is needed
- What will be the ideal line of therapy in myeloma that leads to good outcomes and is cost effective?
- Are there subgroups of myeloma that benefit more?

It will be interesting to see the results of future phase III trials, and especially the eventual CADTH review regarding cost effectiveness.

Related Sessions and Abstracts of Interest:

Sessions for the Engineer

ASH 2020 Abstract 704. Immunotherapies: Therapeutic T cell Manipulation

ASH 2020 Abstract 703. Adoptive Immunotherapy: Mechanisms and New Approaches: Optimizing CAR T cells for Improved Outcomes

ASH 2020 Abstract 801. Gene Editing, Therapy and Transfer

Sessions for the Clinician

ASH 2020 Abstract 626. Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas)—Results from Prospective Clinical Trials: Incorporating novel agents and new adoptive cell therapy approaches

ASH 2020 Abstract 653. Myeloma/Amyloidosis: Therapy, excluding Transplantation: CAR T Therapies for Myeloma: Novel Approaches and Longer-Term Follow Up Data

ASH 2020 Abstract 614. Acute Lymphoblastic Leukemia: Therapy, excluding Transplantation: Chimeric Antigen Receptor T Cell Therapy
Infection with SARS-CoV-2 has been associated with an inflammatory and prothrombotic state with involvement of immune and coagulation systems. Pathophysiology may include pulmonary arterial thrombosis in addition to embolism; Laboratory markers of increased fibrin, FDPs, fibrinogen and D-dimer are associated with worse clinical outcomes. Recent reports have indicated an increased incidence of thromboembolic disease in hospitalized patients, particularly in those who are critically ill. This section provides an overview of relevant trial data on COVID-19 and thromboembolism and Canadian perspectives on these findings from Dr. Lim.

ASH 2020 Abstract 581. Thrombosis, Bleeding, and the Effect of Anticoagulation (AC) on Survival in Critically Ill Patients with COVID-19 in the United States  
Hanny Al-Samkari, MD, et al.

Abstract Summary:
- Multicentre cohort study, n=3239 critically ill patients with COVID-19
- All centers used, at minimum, standard prophylactic doses of AC for critically ill patients with COVID-19
- During the first 14 days of ICU admission:
  - 204 (6.3%) developed radiographically confirmed VTE
  - 90 (2.8%) had major bleeding
  - 48 (1.5%) developed DIC
  - 18 (0.6%) developed HIT
  - Mortality in patients with VTE (38.2%) was similar to the cohort, 71.1% of patients with major bleeding died within 28 days
- Predictors of VTE: male sex, BMI 40 vs <30, D-dimer >10,000 vs <10,000 ng/mL
- Among 2809 patients included in the target trial emulation:
  - 384 (11.9%) received therapeutic AC in the first two days of ICU admission
  - Patients who received therapeutic AC had similar risk of death as those who did not (HR 1.12, 0.92-1.35), similar results across subgroups (age, sex, BMI, mechanical ventilation, D-dimer)

ASH 2020 Abstract 577. Increasing Doses of Anticoagulation Are Associated with Improved Survival in Hospitalized COVID-19 Patients  
Filip Ionescu, MD, et al.

Abstract Summary:
- Retrospective multicentre cohort study, consecutive COVID-19 patients admitted Mar 13-May 5, 2020 to 8 hospitals in Michigan
- N=3480 patients
- Patients were classified as no anticoagulation (AC), prophylactic AC or at least 3 days of therapeutic AC, assessed major bleeding
  - Prophylactic: n=2121 (60.9%)
  - Therapeutic: n=998 (28.7%)
  - No AC: n=361 (10.4%)
AC associated with reduced risk of death compared to no AC

- Prophylactic AC: HR 0.35 (0.22-0.54)
- Therapeutic AC: HR 0.14 (0.05-0.23)

Major bleeding more frequent with therapeutic anticoagulation compared to:

- No anticoagulation: 81 (8.1%) vs 20 (5.5%)
- Prophylactic AC: 81 (8.1%) vs 46 (2.2%)

ASH 2020 Abstract 514. Impact of Treatment and Anticoagulation on Thrombosis in COVID-19 Patients
Surbhi Warrior, MD MPH, et al.

Abstract Summary:

- Single centre, retrospective analysis of COVID-19 (C-19) patients hospitalized between Mar-June 2020 (Chicago)
- N=1265 C-19 positive hospitalized patients
- 138 (10.9%) had thromboembolism
  - Higher rates in C-19 positive than non-C-19 hospitalized patients as reported by CDC: VTE (6.3% vs 0.24%), DVT (5.6% vs 0.15%), PE (4.8% vs 0.12%)
  - In patients with C-19, mortality for patients with thrombosis higher than in patients without thrombosis (31.9% vs 10%, p<0.001)
- Incidence of thrombosis less in patients treated with steroids (14%) compared to other treatments; Tocilizumab 25%, HCQ 42%, Remdesivir 72%

Figure. Effect of Prophylactic vs. therapeutic anticoagulation on mortality rate in hospitalized COVID-19 patients

Limitations: single centre study, unclear number of ICU vs medical patients, whether screening performed, effect of treatments on mortality
ASH 2020 Abstract 206. Anticoagulant and Antiplatelet Use Not Associated with Improvement in Severe Outcomes in COVID-19 Patients
Gwendolyn Ho, MD, MAS, et al.

Abstract Summary:

- Retrospective cohort study of C-19 positive patients between Feb 25-May 8, 2020
- N=2972 patients
- After adjusting for sociodemographic and clinical characteristics, chronic AC or AP use was not associated with a lower risk of any primary outcome (OR 1.03, 0.74-1.45); higher risk of severe outcomes in older age, Asian or Hispanic ethnicity, male gender, obesity, hypertension, diabetes
- Lower risk patient population (positive C-19 test, not necessarily hospitalized)

Related Abstracts of Interest:

Abstract 443. Thromboembolic Outcomes of Hospitalized COVID-19 Patients in the 90-Day Post-Discharge Period: Early Data from the Northwell CORE-19 Registry
Dimitrios Giannis, MD, MSc, et al.

Conclusions and CARE™ Faculty Canadian Perspectives

The anticoagulant dose to prevent VTE remains controversial, with conflicting results on the efficacy of increased dose. We await results of ongoing trials for more clarity.

Predictors of VTE in COVID-19 patients include male sex, obesity, elevated D-dimer; bringing to questions if there is a role for individualized risk assessment or weight-adjusted prophylaxis.

From a Canadian perspective, it is recommended that you continue to follow institutional protocols for prophylaxis or (expert) guidelines on COVID-19 management and enroll patients in clinical trials when possible.

Additional CARE™ Resources for Managing patients during COVID-19:
CARE™ Hematology COVID-19 Guidance with guidance for CLL & MM

CLICK HERE TO SEE THE REPORTS
It is an exciting time in the world of acute leukemia. Advances in patient assessment have allowed for a more personalized approach to treatment based on individual patient characteristics. Dr. Stakiw provides a review of clinical trial data from ASH in AML and ALL that will impact current practice in Canada.

**Acute Myeloid Leukemia (AML)**

ASH 2020 Abstract 635. Five-Year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML): Outcomes By Age Subgroup and Among Responders

*Jeffrey E. Lancet et al.*

**Abstract Summary:**
- 309 patients were randomized to CPX-351 (n = 153) or 7+3 (n = 156)
- The Kaplan-Meier–estimated survival rates were higher for CPX-351 versus 7+3 at 3 y (21% vs 9%) and 5 y (18% vs 8%)
- After a reverse Kaplan-Meier–estimated median follow-up of 60.65 mo (10th to 90th percentile: 58.22, 63.90), improved median OS with CPX-351 versus 7+3 was maintained (9.33 vs 5.95 mo; HR = 0.70 [95% CI: 0.55, 0.91]), with an HR that was very stable and consistent with the prior primary endpoint analysis (9.56 vs 5.95 mo; HR = 0.69 [95% CI: 0.52, 0.90])
- HCT was received by 53 (35%) and 39 (25%) patients in the CPX-351 and 7+3 arms, respectively
- CR or CRi was achieved by 73 (48%) and 52 (33%) patients in the CPX-351 and 7+3 arms, respectively
- The most common primary cause of death was progressive leukemia in both arms (CPX-351: 56%; 7+3: 53%)

**Conclusions and CARE™ Faculty Canadian Perspectives**

After 5 years of follow-up, there was improved OS with CPX-351 vs 7+3 regardless of age, transplant, and achievement of CR/Cri. Longer OS in those who received a transplant or achieved a CR/Cri suggests that deeper responses may be achieved with CPX-351. CPX-351 also can produce or contribute to long-term remissions and survival in older patients with newly diagnoses high risk/secondary AML.

ASH 2020 Abstract 273. Molecular Predictors and Effectiveness of Measurable Residual Disease (MRD) Eradication with Chemotherapy and Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia

*Maximilian Stahl et al.*

**Abstract Summary:**
- 233 patients underwent induction chemotherapy with a baseline NGS
  - Anthracycline + cytarabine +/- an investigational agent
- 142/233 Patients went to Allo SCT
- Allo SCT resulted in high rates of conversion from MRD positive and persistent disease to MRD negative
  - 76% CR/CRI and 64% persistent disease
- Despite early MRD positive to negative conversion post Allo SCT, those NOT MRD negative prior to transplant had a higher incidence of relapse and poorer OS
- Molecular predictors of achieving MRD negative CR-Cri prior to allo-SCT:
  - High rates of MRD negative: NPM1, IDH1, KRAS
  - Decreased odds of MRD- prior to transplant: RUNXI, TP53, SF3B1

Full presentation slides and On Demand video content can be accessed at: [https://careeducation.ca/events/care-at-ash-on-demand-dr-julie-stakiw/](https://careeducation.ca/events/care-at-ash-on-demand-dr-julie-stakiw/)
Delays in Time to Deterioration of Health-Related Quality of Life Were Observed in Patients with Acute Myeloid Leukemia Receiving Venetoclax (VEN) in Combination with Azacitidine (AZA) or in Combination with Low-Dose Cytarabine (LDAC)

Keith W. Pratz et al.

Abstract Summary:
- Viale-A and Viale-C included treatment-naïve pts with AML, ≥18 years of age, and ineligible to receive intensive chemotherapy
- Patients were randomized 2:1 to receive VEN +AZA or placebo (PBO)+AZA in Viale-A, and VEN+LDAC or PBO+LDAC in Viale-C

Viale-A:
- Included 431 pts (VEN+AZA: 286, PBO+AZA: 145)
- Non-statistically significant trend to longer TTD in QoL and fatigue
- Significantly longer TTD in physical functioning and health status

Viale-C:
- Included 211 pts (VEN+LDAC: 143, PBO+LDAC: 68)
- Significantly longer TTD in QoL, fatigue, and physical functioning
- Trend in health status

Table. Cox Proportional Hazards Models: Time to Deterioration in Overall Health/QoL, Physical function, and Fatigue in Viale-A and Viale-C

<table>
<thead>
<tr>
<th>PRO Measure</th>
<th>Viale-A</th>
<th>Viale-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VEN+AZA (n=286)</td>
<td>PBO+AZA (n=145)</td>
</tr>
<tr>
<td>EORTC QLC-Q30 GHS/QoL</td>
<td>16.5 (9.76, NE)</td>
<td>9.3 (4.67, 16.60)</td>
</tr>
<tr>
<td>EORTC QLC-Q30 PF</td>
<td>9.7 (6.71, 16.01)</td>
<td>6.2 (4.67, 9.47)</td>
</tr>
<tr>
<td>PROMIS Fatigue</td>
<td>9.3 (7.17, 16.64)</td>
<td>8.6 (4.18, 16.60)</td>
</tr>
<tr>
<td>EQ-5D-5L VAS</td>
<td>10.7 (7.53, 18.64)</td>
<td>3.9 (2.37, 7.40)</td>
</tr>
</tbody>
</table>

*P<0.01. **P<0.001.
AZA, azacitidine; CI, confidence interval; EORTC QLC-Q30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GHS, global health status; HR, hazard ratio; LDAC, low-dose cytarabine; NE, not estimable; PBO, placebo; PF, physical functioning; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; VAS, visual analog scale; VEN, venetoclax.

The CARE™ Faculty reported on results from the Viale-A and Viale-C trials earlier this year from the ASCO and EHA 2020 virtual annual meetings. Click here to see more!
Conclusions and CARE™ Faculty Canadian Perspectives

For AML patients who are ineligible for intensive chemotherapy and those with a poor prognosis, HRQoL is important when evaluating new treatment regimens. Modelling demonstrated consistently longer TTD in all PRO measures for the venetoclax arms compared to placebo in both trials.

Venetoclax conveys meaningful benefit in terms of HRQoL.

Related AML Abstracts of Interest:

Eunice Wang et al.

ASH 2020 Abstract 459. Comparison of Subcutaneous Injection Versus Intravenous Infusion of Cytarabine for Induction Therapy in Young Ad It Acute Myeloid Leukemia: Results of a Prospective, Multicenter, noninferiority, Randomized Trial
Huafeng Wang et al.

Acute Lymphocytic Leukemia (ALL)

ASH 2020 Abstract 269. Pre-CAR Blinatumomab Is Associated with Increased Post-CD19 CAR Relapse and Decreased Event Free Survival
Agne Taraseviciute et al.

Abstract Summary:

• Retrospective, multicenter study: r/r ALL <25 years old at diagnosis
  • Primary objective: Relapse Free Survival and Event Free Survival at 6 months post CAR infusion
  • 420 patients from 7 centers
  • With a median potential follow-up of 2.3 years (IQR, 1.6-3.3 years), 164 (43.7%) patients experienced relapse
  • The 6-month RFS for blina and non-blina patients was 63.4% (95% CI, 49.6-74.4%) and 81.1% (95% CI, 76.3-85.0%), respectively
  • The 6-month EFS for blina and non-blina patients was 49.7% (95% CI, 37.8-60.5%) and 72.1% (95% CI, 67.1-76.6%), respectively
  • Amongst 408 patients with pre-CAR CD19 analysis, 6/69 (13.0%) of blina patients versus 21/339 (6.2%) of non-blina patients had
    CD19 dim/partial/negative disease (p=0.07)

Conclusions and CARE™ Faculty Canadian Perspectives

Both CD19 CAR T cells and Blinatumomab (blina) induce remission in patients with relapsed/refractory B-cell ALL.

Results from this trial demonstrated an increased risk of CAR non-response, worse RFS and EFS, trend towards higher incidence of pre-CAR CD19 dim disease, and blina non-responders had lower remission rate to CD19 CAR.

Related AML Abstracts of Interest:

ASH 2020 Abstract 162. CAR2.0 Therapy for the Management of Post-Transplantation Relapse of B-Cell Acute Lymphoblastic Leukemia
Rui Zhang et al.
Dr. Soulières provided a review of key late breaking and oral abstracts from ASH in three areas:

- Idiopathic thrombocytopenic purpura (ITP)
- Hemophilia B (HB)
- Sickle Cell Disease

A summary of the abstracts and Dr. Soulières' augmented with additional Canadian perspective follows.

**Idiopathic thrombocytopenic purpura (ITP)**


*Charlotte A Bradbury et al.*

Abstract Summary:

- 120 ITP patients (52.4% male, mean age 54 years, range 17-87), mean baseline platelet count was 7 x10^9/L
- Mean follow up was 18 months (maximum follow up 24 months, minimum follow up of 12 months)
- TTF (Figure): 22% MMF vs 44% No MMF, aHR=0.41 [0.21, 0.80], p=0.0064
  - Excluding secondary ITP: aHR0.37 [0.19, 0.71] p=0.0029

Figure 1: Kaplan Meier graph showing the proportion of patients without treatment failure

No difference in:

- SAEs
- Bleeding events
- Rescue treatments
- Hospital Admissions

Some aspects of quality of life (QoL) were worse in those patients assigned to the MMF:

- Physical role
- Physical function
- Fatigue
Conclusions and CARE™ Faculty Canadian Perspectives

This was the first trial evaluating the combination of steroids plus MMF for ITP and demonstrated a reduction in half of refractory and relapsed cases. It seems to be applicable to patients of any age and may be considered as an alternative to steroids.

These results indicate there might be a consideration for a possible reduction in QoL so further studies required. It also remains to be seen what the effect on TTF2 will be with this approach.

Other Abstracts of Interest in ITP

ASH 2020 Abstract 22. Oral Rilzabrutinib, a Bruton Tyrosine Kinase Inhibitor, Showed Clinically Active and Durable Platelet Responses and Was Well-Tolerated in Patients with Heavily Pretreated Immune Thrombocytopenia
David J. Kuter et al.

ASH 2020 Abstract 23. Long-Term Safety and Efficacy of Sutimlimab in Patients with Chronic Immune Thrombocytopenia
Catherine M. Broome et al.

Hemophilia B

ASH 2020 Abstract LBA-6. First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFVIII variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies
Steven W. Pipe et al.

Abstract Summary:
75 patients were screened, of whom 67 entered lead-in. 54 patients were dosed (44 severe, 10 moderately severe HB) and completed 26wks of follow-up.
Mean age (±SD) was 41.5 (15.8) yrs. 38/54 patients (70.4%) had bleeds (n=123) during the lead-in despite prophylaxis, and 23/54 (42.6%) had Nabs to AAV5 at baseline (max titer: 3212.3).
Post-treatment:
• FIX activity increased to a mean (SD; min, max) of 37.2% (±19.6; 1.0, 97.1) at wk26
  • Change from baseline of 36.0% ±19.7; 0, 96.1p<0.0001, confirmed
  • No correlation of pre-existing Nabs with FIX activity was identified up to a titer of 678.2; n=52, R2= 0.078
    • A single patient had a Nab titer of 3212.3 and did not respond
    • One other patient received a partial dose and remained on prophylaxis
  • 52/54 patients (96.3%) discontinued routine prophylaxis
  • 39/54 (72.2%) patients reported0 bleeds in the first 26wks post-treatment
  • 15 patients reported a total of 21 bleeds
• Factor consumption (Mean(SD) annualized consumption IU/y/pt:
  • Pre-treatment: 292,304 (±171,079)
  • Post-treatment: 12,622 (±36,466) at wk26 (96.0% reduction)
Adverse events:

- Any: 37/54 (68.5%) patients
- Mild: 81.5%
- No deaths occurred
- No treatment-related SAEs
- 7 patients had infusion-related reactions; the infusion was discontinued in 1 patient
- Elevation of ALT/AST: 9 patients
  - Steroids per protocol. All discontinued steroid use: prior to wk26
  - FIX activity was preserved in the mild range
- Most frequent AEs: headache (13.0%), influenza-like illness (13.0%)
- No inhibitors to FIX were reported
- No relationship between safety and Nabs was observed

Conclusions and CARE™ Faculty Canadian Perspectives

Efficacy is proven in this study with sustained FIX production, no inhibitors, and a reduction in bleeding episodes. There is no confirmed relationship of AAV 5 Nabs.

This is a disease modifying therapy for Hemophilia B should become a standard of care but will require additional procedures to be put in place for tracking outcomes longer-term.

Sickle Cell Disease

ASH 2020 Abstract 369. Evidence of Educational Bias in Cognitive Screening of Adults with Sickle Cell Disease: Comparison of Available Tools and Possible Strategies for Mitigation
Stéphanie Forté et al.

Abstract Summary:

- Primary aim: compare the prevalence of abnormal RUDAS and MoCA scores in adult SCD patients
- Secondary aims: examine for the presence of educational bias; develop mitigation strategies in case of such a bias
- Cross sectional study, UMGGR (Henri Mondor Hospital, Créteil)
- Inclusion criteria: outpatients ≥18 years old; all SCD phenotypes
- Exclusion criteria: inability to obtain informed consent and/or follow study instructions
- Intervention: Cognitive screening using
  - French translation of RUDAS
  - MoCA (third alternative version)
  - Additional visuospatial task of copying overlapping triangles, derived from the French BEC96 assessment
  - Anxiety and depression using the Hospital Anxiety Depression Scale (HADS)
  - Survey on demographics and education
Cognitive impairment is a dreaded complication of sickle cell disease (SCD). Guidance on the optimal screening strategy is lacking and several available tools are biased by language and education.

Takeaways from this study:
- RUDAS and MoCA both showed high prevalence of suspected cognitive impairment in adult SCD patients
- RUDAS and MoCA showed education bias when applied to adult SCD patients
- RUDAS was less biased overall but visuospatial assessment remained biased
- Adjusting RUDAS by education allows systematic identification of SCD patients in need of comprehensive neurocognitive testing

Prospective validation of these findings is ongoing.
Other Abstracts of Interest in SCD

ASH 2020 Abstract 13. Randomized Controlled Trial of Fixed Low-Vs Moderate-Dose Hydroxyurea for Primary Stroke Prevention in Sub-Saharan Africa: Final Results of the Spring Trial
Shehu Umar Abdullahi et al.

Shehu Umar Abdullahi et al.

ASH 2020 Abstract 302. 302 COVID-19 Outcomes in Individuals with Sickle Cell Disease and Sickle Cell Trait Compared to Blacks without Sickle Cell Disease or Trait
Ashima Singh et al.

Click Here to see the CARE™ Navigation Guide with more ASH abstracts in benign hematology highlighted by Dr. Soulières!

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